ORIGINAL ARTICLE

Evaluation of the association between serum uric acid level and the predicted risk score of sudden cardiac death in five years in patients with hypertrophic cardiomyopathy

Hipertrofik kardiyomiyopatili hastalarda serum ürik asit seviyesi ile öngörülen beş yıllık ani kardiyak ölüm risk skoru arasındaki ilişkinin değerlendirilmesi

Sinem Özyılmaz, M.D.,[1] Muhammet Hulusi Satılmışoğlu, M.D.,[1] Mehmet Gül, M.D.,[1] Hüseyin Uyarel, M.D.,[2] Osman Akin Serdar, M.D.[3]

[1]Department of Cardiology, Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital, İstanbul, Turkey

[2]Department of Cardiology, Bezmialem Vakıf University Faculty of Medicine, İstanbul, Turkey

[3]Department of Cardiology, Uludağ University Faculty of Medicine, Bursa, Turkey

ABSTRACT

Objective: The aim of this study was to determine the relationship between serum uric acid (UA) level and the predicted risk score for sudden cardiac death in 5 years (the HCM Risk-SCD), galectin-3 level, and positive fragmented QRS (fQRS) on electrocardiography (ECG) in patients with hypertrophic cardiomyopathy (HCM).

Methods: This was a prospective, observational study. In all, 115 consecutive patients (age >17 years) with HCM and 80 healthy participants were included in the study. The HCM Risk-SCD score (%), galectin-3 level, and fQRS on ECG were evaluated in all patients.

Results: The serum UA, galectin-3 level, UA/Creatinine ratio, incidence of ventricular tachycardia (VT) and syncope, and some echocardiographic parameters were significantly higher in the patient group than in the control group (all p<0.05). The UA value was significantly higher in patients with a high score on the HCM Risk-SCD, a positive fQRS, a high galectin-3 level, VT incidence, and need for implantable cardioverter defibrillator (ICD) implantation or cardiopulmonary resuscitation (CPR) than in those without (HCM Risk-SCD >6%. Namely, HCM Risk-SCD >6%, UA: 6.71±1.29 mg/dL, HCM Risk-SCD ≤5.9%, UA: 5.84±1.39 mg/dL, p=0.001; fQRS(+), UA: 6.56±1.20 mg/dL, fQRS(-), UA: 5.63±1.49 mg/dL, p<0.001; galectin-3 >6.320 pg/mL, UA: 6.56±1.27 mg/dL, galectin-3 ≤6.310 pg/mL, p=0.016; left atrium anterior-posterior dimension (LAAPD) >36 mm, UA: 6.31±1.33 mg/dL, LAAPD <36 mm, UA: 5.20±1.60 mg/dL, p=0.005; VT(+), UA: 6.83±1.19 mg/dL, VT(-), UA: 5.97±1.42 mg/dL, p=0.008; ICD(+), UA: 7.08±0.88 mg/dL, ICD(-), UA: 6.06±1.42 mg/dL, p=0.022; CPR(+), UA: 7.03±0.96 mg/dL, CPR(-), UA: 6.04±1.42 mg/dL, p=0.018. A statistically significant correlation was observed between UA and HCM Risk-SCD, galectin-3 level, LAAPD, and left ventricular (LV) mass (LVM) (r and p values, respectively: 0.355, <0.001; 0.297, 0.002; 0.309, 0.001; 0.276, 0.003.

Conclusion: The serum UA level was significantly higher in patients with HCM compared with the control group. A high UA level was associated with a higher HCM Risk-SCD score, positive fQRS, higher galectin-3 level, greater LAAPD, VT incidence, and the need for ICD implantation and CPR in patients with HCM.

ÖZET

Amaç: Bu çalışmanın amacı hipertrofik kardiyomiyopati (HKM) bulunan hastalarda serum ürik asit (ÜA) seviyesi ile öngörülen beş yıllık ani kardiyak ölüm riski (HKM-AKÖ) skoru (%), galektin-3 düzeyi, elektrokardiyografi'de (EKG) fragmente QRS (fQRS) pozitifliği arasında ki ilişkiyi belirlemektir.

Yöntemler: Bu ileriye dönük gözlemsel bir çalışmadır. Çalışmaya, ardışık 115 HKM'li hasta ve 80 sağlıklı birey dahil edildi. Tüm hastaların HKM-AKÖ risk skoru, galektin-3 düzeyi, EKG'de fQRS varlığı değerlendirildi.

Bulgular: Serum ÜA, galektin-3 düzeyi, ÜA/Kreatinin (Kr), ventriküler taşikardi (VT) and senkop sıklığı, bazı ekokardiyografi parametreleri hasta grubunda kontrol grubuna göre anlamlı derecede yüksekti (tüm p<0.05). Serum ÜA düzeyi, yüksek HKM-AKÖ risk skoru, pozitif fQRS, yüksek galektin-3 düzeyi, VT insidansı, yerleştirilebilir kardiyovertör defibrilator (YKD), kardiyopulmoner canlandırma (KPC) ihtiyacı yüksek olan hastalarda olmayanlara göre anlamlı olarak yüksek bulundu (HKM-AKÖ risk >%6, ÜA: 6.71±1.29 mg/dL, HKM-AKÖ risk ≤%5.9, ÜA: 5.84±1.39 mg/dL, p=0.001; fQRS(+), ÜA: 6.56±1.20 mg/dL, fQRS(-), ÜA: 5.63±1.49 mg/dL, p<0.001; galektin-3 >6.320 pg/mL, UA: 6.56±1.27 mg/dL, galectin-3 ≤6.310 pg/mL, ÜA: 5.90±2.43 mg/dL, p=0.016, sol atriyum ön-arka çap (SAAPÇ) >36 mm, ÜA: 6.31±1.33 mg/dL, SAAPÇ <36 mm, ÜA: 5.20±1.60 mg/dL, p=0.005; ventriküler taşikardi (VT)(+), ÜA: 6.83±1.19 mg/dL, VT(-), ÜA: 5.97±1.42 mg/dL, p=0.008; YKD(+), ÜA: 7.08±0.88 mg/dL, YKD(-), ÜA: 6.06±1.42 mg/dL, p=0.022; KPR(+), ÜA: 7.03±0.96 mg/dL, KPR(-), ÜA: 6.04±1.42 mg/dL, p=0.018). ÜA düzeyi ile HKM-AKÖ risk skoru, galektin-3 düzeyi, sol atriyum ön arka çap (SAÖAÇ), sol ventrikül kütle'si (SVK) arasında anlamlı korelasyon bulundu [sırasıyla r ve p değerleri 0.355; <0.001, 0.297; 0.002, 0.309; 0.001, 0.276; 0.003]).

Sonuç: Hipertrofik kardiyomiyopatili hastalarda serum ÜA düzeyi kontrol grubu ile karşılaştırıldığında anlamlı olarak yüksekti. HKM'li hastalarda yüksek ÜA seviyesi ile yüksek HKM-AKÖ risk skoru, fQRS pozitifliği, galektin-3 düzeyi, SAAPÇ, VT sıklığı, YKD ve KPR gereksinimi arasında anlamlı ilişki saptanmıştır.

Received: April 09, 2017 *Accepted:* October 24, 2017

Correspondence: Dr. Sinem Özyılmaz. Mehmet Akif Ersoy Göğüs Kalp ve Damar Cerrahisi Eğitim ve Araştırma Hastanesi, Kardiyoloji Kliniği, İstanbul, Turkey.
Tel: +90 212 - 692 20 00 / 1134 e-mail: drsinemozbey@gmail.com

Hypertrophic cardiomyopathy (HCM) is a relatively common genetic heart disease and an important cause of sudden cardiac death (SCD), especially in the young.[1] Despite the large number of studies, no laboratory or imaging method has been found that can precisely determine the risk of SCD in HCM patients. A family history of SCD, the maximum wall thickness of the left ventricle (LV), non-sustained ventricular tachycardia (VT), a left ventricular outflow tract obstruction gradient (LVOTOG) and unexplained syncope have been determined to be risk factors for SCD in HCM.[1,2] However, which of these variables is more important in the estimation of the risk of SCD, or the significance of the presence of other factors in addition to these has not yet been elucidated. The latest European Society of Cardiology (ESC) guideline for HCM included a new method to predict SCD risk in an effort to resolve confusion. The prediction of 5-year risk of SCD using the HCM Risk-SCD is a practical method developed to identify especially high-risk patients.[3]

Abbreviations:

CPR	*Cardiopulmonary resuscitation*
Cr	*Creatinine*
ECG	*Electrocardiogram*
fQRS	*Fragmented QRS*
HCM	*Hypertrophic cardiomyopathy*
ICD	*Implantable cardioverter defibrillator*
IVST	*Interventricular septum thickness*
LA	*Left atrium*
LAAPD	*LA anterior-posterior dimension*
LAV	*LA volume*
LAVI	*LA volume index*
LV	*Left ventricle*
LVEDD	*LV end-diastolic diameter*
LVEF	*LV ejection fraction*
LVESD	*LV end-systolic diameter*
LVM	*LV mass*
LVMI	*LVM index*
LVOTO	*LV outflow tract obstruction*
LVPWT	*LV posterior wall thickness*
LVOTOG	*LV outflow tract obstruction gradient*
SCD	*Sudden cardiac death*
UA	*Uric acid*
UA/Cr	*UA/Creatinine ratio*
VT	*Ventricular tachycardia*
XO	*Xanthine oxidase*

Recently, some opinions claiming that abnormal fibrosis associated with HCM has triggered ventricular arrhythmias have gained importance, and studies have progressed in this direction. Some of the methods to evaluate cardiac fibrosis are the measurement of galectin-3 and fragmented QRS (fQRS). Galectin-3 is a beta-galactoside-binding lectin expressed by macrophages. Recent studies have shown that the level of galectin-3 increases in diseases associated with cardiac inflammation and fibrosis.[4] The fQRS complex seen on a 12-lead electrocardiogram (ECG) is associated with myocardial fibrosis and high risk of SCD in HCM patients.[5,6]

The serum uric acid (UA) level is the end product of purine catabolism and triggers purine degradation, causing hypoxia. An elevated serum UA level has been shown to be an independent predictor of incidence and adverse cardiovascular outcomes in some cardiovascular diseases.[7,8] A recent study demonstrated that the serum UA level was a prognostic indicator for patients with HCM,[9] but thus far there is no study revealing a relationship between UA level and the HCM-Risk SCD. The aim of this study was to investigate the relationship between the HCM Risk-SCD and UA level and to assess the relationship between UA and cardiac fibrosis.

METHODS

Study population

In this prospective observational study, we included 115 consecutive patients (age >17 years) with HCM presenting to the Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Center, Training and Research Hospital and Bezmialem Vakıf University, School of Medicine between December 2012 and March 2016.. Long-term follow-up results of patients with HCM were evaluated in this study. The study was approved by the ethics committee (date: April 8, 2015; reference no: 7/7) of Bezmialem Vakıf University, School of Medicine. All patients signed an informed consent form. This study was performed in accordance with the requirements of the Declaration of Helsinki.

The study inclusion criteria were as follows: age >17 years, echocardiography (n=49) and/or cardiac magnetic resonance imagery revealing HCM (n=66), which was defined as a maximum LV wall thickness ≥15 mm, and 1 or more LV myocardial segments that could not be explained by abnormal loading conditions.[1] In cases of a smaller degree of wall thickening (13–14 mm), other factors were evaluated, including family history, positive gene mutations, and electrocardiogram (ECG) abnormalities.

Patients who were lost to follow-up (n=2), or who had missing UA level measurements, uncontrolled hypertension (n=8), renal failure (n=2), aortic valve stenosis (n=1), a previous myocardial infarction history (n=1), septal ablation procedure (n=4), or septal myomectomy (n=1) were excluded from the study. Patients known to have critical coronary artery stenosis were not included. Furthermore, patients with

diseases that could affect the serum UA level (malignancy, hypoxanthine-guanine phosphoribosyl transferase enzyme deficiency, chronic renal failure, gout, psoriasis), and those who used drugs (salicylates, thiazide diuretics, allopurinol, cytotoxic drugs, ethambutol, and pyrazinamide etc.) or alcohol were also excluded. In this study group, diuretic treatment was not routine therapy at the outpatient clinic due to the possibility of reducing end-diastolic volume and increasing the LVOTOG, as suggested by ESC guidelines. The final study population consisted of 115 patients.

Details of patient medical history, family history of SCD, history of syncope, and a special questionnaire on lifestyle and risk factors were obtained at admission.

Measurement of plasma uric acid level

A complete blood count and other serum values were determined. The plasma UA (mg/dL) level was measured at the first polyclinic control visit. The separated plasma of all patients, the UA, and other blood materials were stored at -50°C until testing was performed. The plasma UA level was calculated using the enzymatic colorimetric method with a commercial kit (Roche Diagnostics, Basel, Switzerland) and the Roche/Hitachi Cobas 6000 analyzer (Roche Diagnostics, Basel, Switzerland). The UA/Creatinine (UA/Cr) ratio was calculated for each patient. As a biochemical variable, total cholesterol was also calculated with the auto-analyzer.

Measurement of plasma galectin-3 level

Serum galectin-3 (pg/mL) was measured in duplicate using a commercially available enzyme-linked immunosorbent assay method (Human galectin-3 ELISA kit, catalogue no. DGAL30; R&D Systems, Inc., Minneapolis, MN, USA). The intra-observer variability in the measurement of galectin-3 was also assessed, and all of the mean intra-assay coefficients of variance were less than 4.6.[10] The patients were divided into 2 groups: galectin-3 level ≤6.310 pg/mL and >6.320 pg/mL.

Electrocardiography

A resting, 12-derivation surface ECG was obtained from all patients in the supine position. The ECG recordings were made using a Nihon Kohden-Cardiofax S device (ECG-1250K, filter range 0.5 Hz to 150 Hz, AC filter 60 Hz, at a speed of 25 mm/second and an amplitude of 10 mm/mV; Nihon Kohden, Tokyo, Japan) at the first visit. The rhythm, speed, and presence of arrhythmia were assessed.

Fragmented QRS measurement

Two independent readers who were blinded to the final comment evaluated the presence or absence of fQRS. The interindividual agreement on the interpretation of the presence of fQRS was 96.8% (j=0.93). fQRS was defined as the presence of an extra R wave (R1) with or without Q wave in a 12-lead ECG, the presence of notching on an R wave, the presence of notching on an S wave, or the presence of more than one R1 wave in 2 adjacent derivations corresponding to the feeding area of one of the major coronary arteries.[6]

Echocardiography

Upon hospital admission, a transthoracic echocardiographic study was performed using a Vivid S5 3S-RS probe (General Electric Vivid S5; GE Vingmend Ultrasound AS, Horten, Norway) with a 1.7/3.4 MHz phased-array transducer, and the LV ejection fraction (LVEF)(%) was calculated using the biplane Simpson method.[11] The thicknesses of the LV wall [interventricular septum thickness (IVST) and LV posterior wall thickness (LVPWT)] was measured along the parasternal long axis. The LV outflow tract obstruction (LVOTO) gradient was measured using the apical 5-chamber view. The maximum LV outflow gradient was determined at rest with Valsalva provocation. In addition, LV end-diastolic diameter (LVEDD)(mm), end-systolic diameter (LVESD) (mm), left atrial (LA) anterior-posterior diameter (LAAPD), LA volume (LAV) (mL), LA volume index (LAVI) (mL/m^2), LV mass (LVM) (g), and LVM index (LVMI) (g/m^2) were calculated according to the Devereux formula using M-mode images.[12] The patients were divided into 2 groups: LAAPD ≤35.9 (mm) and >36 (mm). Mitral valve regurgitation (systolic anterior motion of the mitral valve), and LV diastolic dysfunction were also assessed.

Holter electrocardiography

The 12-channel recordings obtained from ambulatory Holter ECG monitors (DMS 300-7 Holter Reader; DM Software, Stateline, NV, USA) worn for 24 hours were analyzed. Before automatic analysis, the tapes were evaluated using the Holter program (CardioScan 12.0; DM Software, Stateline, NV, USA). The record-

ings were assessed for rhythm, supraventricular extrasystole, supraventricular tachycardia, paroxysmal atrial fibrillation, ventricular extrasystole, VT, and atrioventricular block with pauses.

Measurement of the predicted Hypertrophic Cardiomyopathy Risk-Sudden Cardiac Death score in the patients

The probability of SCD (the HCM Risk-SCD score) for an individual patient can be calculated using the following equation derived from the Cox proportional hazards model:

Predicted SCD at 5 years=1–S0(t) exp (Prognostic Index), where S0(t) is the average survival probability at a certain time t (i.e., at 5 years) and the prognostic index is the sum of the products of the predictors and their coefficients.[1,3] Assessment of the HCM Risk-SCD was performed for each patient on the first visit and it was repeated if there was any change in the patient's clinical status or Holter and echocardiography results. Patients were divided into 2 groups according to the HCM Risk-SCD score percentage of ≤5.9% and >6%.

Statistical analysis

Qualitative variables were expressed as percentages (%), and quantitative variables as mean value±SD. Non-parametric values were expressed as median (minimum-maximum). Normally distributed continuous variables were assessed using the Kolmogorov-Smirnov test. The data were considered normally distributed when the p value was greater than 0.05. The Mann-Whitney U test was used to compare non-parametric values between 2 groups. A comparison of parametric values between 2 groups was performed with a 2-tailed independent Student's t-test, and a chi-square test was used to compare rates between groups. Scatter plot graphs were used to evaluate the relationships between the serum UA level, the UA/Cr ratio, and other variables. Pearson's correlation test was used for the variables with a linear correlation, and Spearman's correlation test was used for those without a linear correlation. Logistic regression analysis results were not significant. A p value less than 0.05 was considered statistically significant. All statistical studies were carried out using SPSS for Windows, Version 15.0 (SPSS, Inc., Chicago, IL, USA).

Study endpoints and follow-up

The patients' medical history, family history of SCD, history of syncope, and responses to a special questionnaire on lifestyle and risk factors were recorded at admission. The patients were followed up during visits to the HCM outpatient clinic at regular 3-month intervals. Any change in clinical status was noted. An ECG was performed every 3 months. Holter monitoring for 24 hours was performed at least once in all patients, and at least twice in those with more than 1 risk factor for SCD. Holter monitoring for 24 hours was also performed when patients had any possible arrhythmic symptoms, including dizziness, light headedness, palpitations, or syncope. The primary endpoint for the study was ventricular arrhythmic events. The secondary endpoint was occurrence of major arrhythmic events and death. Follow-up for clinical endpoints was performed by telephone interview and review of outpatient and inpatient medical records.

RESULTS

Baseline characteristics

A total of 115 patients (67 males and 48 females) diagnosed with HCM were included in the patient group, and the control group comprised 80 participants (35 males and 45 females). The participants' demographic and clinical characteristics are summarized in Table 1. There were no significant differences between the patient and control groups with regard to age or body mass index. The medical therapies administered to the participants are shown in Table 1.

The serum UA level (mg/dL), UA/Cr ratio, LVMI (g/m^2), LAAPD (mm), LAVI, LVOTOG$_{max}$ (mm Hg), and the relative wall thickness index were significantly higher in the patient group than in the control group [6.2 mg/dL (2.4–9 mg/dL) *vs*. 4.4 mg/dL (2.6–8 mg/dL), p<0.001; 7.2 (2.9–15.6) *vs*. 6.4 (3.4–8.8), p<0.001; 166 g/m^2 (79–400 g/m^2) *vs*. 77 (45–170 g/m^2), p<0.001; 42 mm (32–53 mm) *vs*. 35 mm (26–45 mm), p<0.001; 28.9 (15–61) *vs*. 4.2 (2.6–8), p<0.001; 20 mm Hg (0–140 mm Hg) *vs*. 0 mm Hg, p<0.001; 0.55 (0.35–1.7) *vs*. 0.38 (0.28–0.56), p<0.001 respectively].

Clinical outcomes

The mean duration of follow-up was 31.7±12.7 months. Two patients were lost and 33 patients were hospitalized due to worsening symptoms of heart failure. Of the patients, 48 had a family history, 36 had pre-syncope, and 13 had a history of syncope.

Table 1. Baseline and clinical characteristics of the patients and control group

Characteristics of patients	Patient group [n, median (min-max) or mean±SD]	Control group [n, median (min-max) or mean±SD]	*p*
Number of patients (n)	115	80	
Male (n)	67 (58%)	35 (44%)	0.046
Age (years)	45.5 (18–79)	43 (26–64)	0.088
Body mass index (kg/m^2)	27.2±3.7	27.8±4.0	0.060
New York Heart Association class III and IV	24 (20.8%)	0	
Hypertension (n)	5 (4.3%)	13 (17.5%)	0.005
Treatment (n)			
Medical therapy			
Beta-blocker	103 (90.4%)	14 (17.5%)	<0.001
Calcium channel blocker	5 (4.4%)	7 (8.7%)	
Amiodarone	4 (3.5%)	0	
Dysopyramide	8 (7%)	0	
Paroxismal atrial fibrilliation (n)	12 (10.4%)	0	
Blood urea nitrogen	14 (6–48)	11 (7–24)	<0.001
Uric acid (mg/dL)	6.2 (2.4–9)	4.4 (2.6–8)	<0.001
Creatinine (mg/dL)	0.8 (0.4–2.5)	0.7 (0.4–1.2)	<0.001
Uric acid/creatinine ratio	7.2 (2.9–15.6)	6.4 (3.4–8.8)	<0.001
Galectin-3 (pg/mL)	5.613 (1.056–10.500)	2.049 (0.348–6.500)	<0.001
Ejection fraction (%)	68 (26–82)	63.5 (40–67)	<0.001
Left ventricular mass index (g/m^2)	166 (79–400)	77 (45–170)	<0.001
Ventricular tacyhcardia (n)	24 (21%)	0	
Left atrium anterior-posterior dimension (mm)	42 (32–53)	35 (26–45)	<0.001
Left atrium volüme index	28.9 (15–61)	4.2 (2.6–8)	<0.001
LVOTGmax (mm Hg)	20 (0–140)	0	<0.001
Left ventricle end diastolic diameter (mm)	41 (25–58)	44 (39–59)	0.050
Relative wall thickness index	0.55 (0.35–1.7)	0.38 (0.28–0.56)	<0.001
Syncope (n)	13 (11.3%)	0	

LVOTGmax: Left ventricle outflow track maximum gradient; SD: Standard deviation.

Of the patients included, 78 were categorized as New York Heart Association class II (n=54), 24 were class III, and none were class IV. A total of 103 of the patients used beta-blockers, 4 took amiodarone, 8 used disopyramide, and 4 took calcium channel blockers. Diuretic treatment was given only during hospitalization due to cardiac failure. Eleven patients received an implantable cardioverter defibrillator (ICD). Eight of the ICD patients showed appropriate shock and 3 demonstrated inappropriate shock. In all, 13 patients underwent CPR, and it was determined that 24 patients had a VT attack.

Comparisons of UA value were made between different groups according to HCM Risk-SCD, fQRS, galectin-3, LAAPD, VT, ICD implantation, and CPR in the patients with HCM (Table 2). The UA value was significantly higher in patients with a high score on the HCM Risk-SCD, positive fQRS, high galectin-3 level, greater LAAPD, VT, ICD implantation, and CPR than in those without [HCM Risk-SCD >6% (n=41), UA: 6.71±1.29 mg/dL *vs.* HCM Risk-SCD ≤5.9% (n=74), UA: 5.84±1.39 mg/dL, p=0.001; fQRS(+) (n=65), UA: 6.56±1.20 mg/dL *vs.* fQRS(-) (n=50), UA: 5.63±1.49 mg/

Table 2. Comparison of UA value in different groups according to the HCM SCD risk, fQRS, galectin-3, LAAPD, VT, ICD implantation, and CPR application in patients with HCM

Variables		Uric acid	*p*
		Mean±SD	
HCM Risk-SCD	>6% (n=41)	6.71±1.29	0.001
	≤5.9% (n=74)	5.84±1.39	
Fragmented QRS	(+) (n=65)	6.56±1.20	<0.001
	(-) (n=50)	5.63±1.49	
Galectin-3 (pg/mL)	>6.320 (n=49)	6.56±1.27	0.016
	≤6.310 (n=66)	5.90±2.43	
LAAPD (mm)	>36 (n=100)	6.31±1.33	0.005
	≤ 35.9 (n=15)	5.20±1.60	
VT	(+) (n=24)	6.83±1.19	0.008
	(-) (n=91)	5.97±1.42	
ICD implantation	(+) (n=11)	7.08±0.88	0.022
	(-) (n=104)	6.06±1.42	
CPR	(+) (n=13)	7.03±0.96	0.018
	(-) (n=102)	6.04±1.42	

CPR: Cardiopulmonary resuscitation; EF: Ejection fraction; fQRS: Fragmented QRS; HCM Risk-SCD: Predicted risk score of sudden cardiac death at 5 years for hypertrophic cardiomyopathy patients; ICD: Implantable cardioverter defibrillator; LAAPD: Left atrial anterior-posterior dimension; SCD: Sudden cardiac death; UA: Uric acid; VT: Ventricular tachycardia.

dL, p<0.001; galectin-3 >6.320 pg/mL (n=49), UA: 6.56±1.27 mg/dL *vs*. galectin-3 ≤6.310 pg/mL (n=66), UA: 5.90±2.43 mg/dL, p=0.016; LAAPD >36 mm (n=100), UA: 6.31±1.33 mg/dL *vs*. LAAPD ≤35.9 mm (n=15), UA: 5.20±1.60 mg/dL, p=0.005; VT(+) (n=24), UA: 6.83±1.19 mg/dL *vs*. VT(-) (n=91), UA: 5.97±1.42 mg/dL, p=0.008; ICD implantation(+) (n=11), UA: 7.08±0.88 mg/dL *vs*. ICD implantation(-) (n=104), UA: 6.06±1.42 mg/dL, p=0.022; CPR(+) (n=13), UA: 7.03±0.96 mg/dL *vs*. CPR(-) (n=102), UA: 6.04±1.42 mg/dL, p=0.018] (Fig. 1).

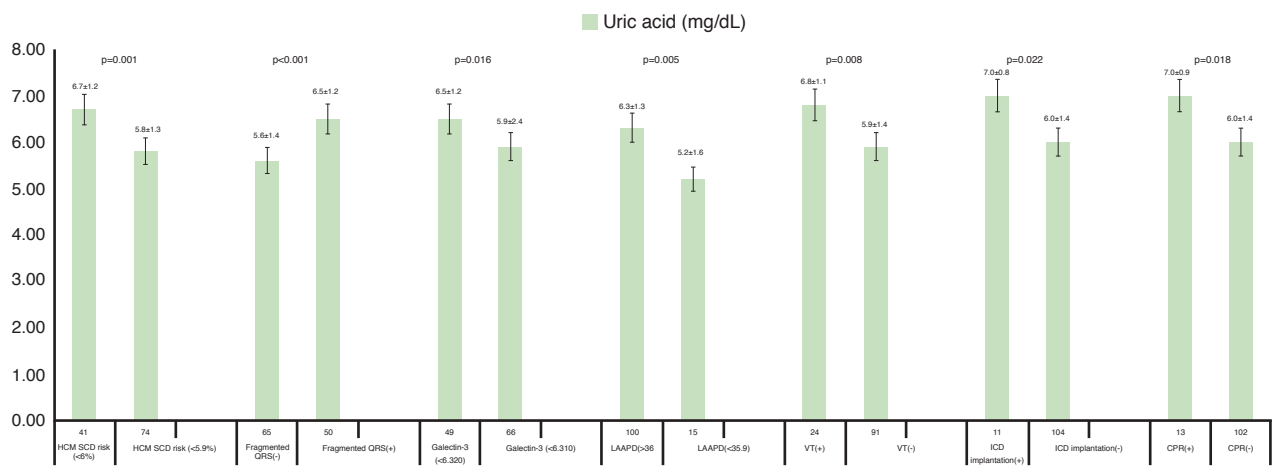

Figure 1. Comparison of UA and HCM SCD risk, fragmented QRS, galectin-3, LAAPD, VT, ICD implantation, and CPR in patients with HCM. CPR: Cardiopulmonary resuscitation; HCM SCD risk: Predicted risk score of sudden cardiac death at 5 years for hypertrophic cardiomyopathy patients; ICD: Implantable cardioverter defibrillator; LAAPD: Left atrial anterior-posterior dimension; UA: Uric acid; VT: Ventricular tachycardia.

Table 3. Correlation between uric acid, uric acid/creatinine ratio and other parameters

Variables	Median (min-max) or mean±SD	Uric acid (mg/dL)		Uric acid/ creatinine	
		6.1±1.4		7.6±2.1	
		r	*p*	r	*p*
HCM Risk-SCD (%)	4.3 (1–24)	0.355	<0.001	0.136	0.153
Galectin-3 (pg/mL)	5.613 (1.056–10.500)	0.297	0.002	0.118	0.229
Corrected QT interval	421 (309–638)	0.188	0.044	0.099	0.295
Body mass index (kg/m^2)	27.2±3.7	0.035	0.710	-0.141	0.135
Left atrial anterior-posterior dimension (mm)	42 (32–53)	0.309	0.001	0.156	0.098
Left atrial mediolateral dimension (mm)	45 (26–66)	0.315	0.001	0.264	0.005
Left atrial volume index (mL/m^2)	28.9 (15–61)	0.319	0.001	0.230	0.014
Left atrial apicobasal dimension (mm)	51 (36–70)	0.398	<0.001	0.209	0.026
Ejection fraction (%)	68 (26–82)	0.038	0.689	0.205	0.030
Interventicular septum thickness (mm)	21 (15–36)	0.199	0.034	0.198	0.036
Left ventricular posterior wall thickness (mm)	12 (8–27)	0.197	0.036	0.141	0.138
Left ventricular end-diastolic diameter (mm)	43 (25–58)	-0.018	0.852	-0.110	0.245
Left ventricular end-systolic diameter (mm)	25.5 (10–43)	-0.029	0.761	0.002	0.980
Left ventricular mass (g)	320 (153–616)	0.276	0.003	0.125	0.186
Left ventricular mass index (g/m^2)	166 (79–400)	0.202	0.031	0.193	0.041
Relative wall thickness index	0.55 (0.35–1.7)	0.122	0.194	0.176	0.062
Age (years)	45.5 (18–79)	-0.148	0.155	-0.158	0.094
Left ventricular outflow track maximum gradient (mm Hg)	20 (0–140)	0.165	0.080	0.118	0.217
C-reactive protein (mg/L)	1.4 (1–35)	-0.092	0.328	-0.068	0.472
Erythrocyte sedimentation rate (mm/h)	8 (1–57)	0.081	0.508	-0.091	0.458

HCM Risk-SCD: Predicted risk score of sudden cardiac death at 5 years for hypertrophic cardiomyopathy patients.

Results of correlations between uric acid, uric acid/creatinine ratio, and other parameters

A statistically significant correlation was observed between UA level and HCM Risk-SCD score (%), serum galectin-3 level, LAAPD, LVPWT, LVM, and corrected QT interval (r and p values, respectively: 0.355, <0.001; 0.297, 0.002; 0.309, 0.001; 0.197, 0.036; 0.276, 0.003; 0.188, 0.044). UA and UA/Cr were also significantly correlated with LAMLD, LAVI, LAABD, LVMI, and IVST (r and p values, respectively: 0.315, 0.001; 0.264, 0.005; 0.319, 0.001; 0.230, 0.014; 0.398, <0.001; 0.209, 0.026; 0.202, 0.031; 0.0193, 0.041; and 0.199, 0.034; 0.198, 0.036). A statistically significant correlation was observed between UA/Cr ratio and EF (r and p values, respectively: 0.205, 0.030) (Table 3). No statistically significant correlation was found between the UA, UA/Cr, and the other parameters.

DISCUSSION

The present study was designed to investigate the correlation between serum UA level and negative events in HCM. The most important results of this study were the following: 1) The UA value was significantly higher in patients with a high score on the HCM Risk-SCD and a statistical significant correlation was observed between UA level and the HCM Risk-SCD. 2) There was a significant relationship between the serum UA level and the serum galectin-3 level. 3) A high UA level seemed to be associated with increased frequency of fQRS, VT, and the requirement for CPR and ICD implantation. 4) A higher serum UA level was correlated with a greater LA diameter and a greater LAVI and LVMI.

There are 2 important factors contributing to elevated concentrations of serum UA. One is an excre-

tion defect due to renal failure, and the other is the production of excess uric acid due to the activation of the xanthine oxidase (XO) system.[13] Serum UA is a product produced by XO system activation in the terminal stage of purine metabolism. Epidemiological studies have shown that an elevated serum UA concentration via XO system activation is associated with oxidative stress formation through inflammatory mediators such as tumor necrosis factor-alpha and mitogen-activated protein kinases.[14] Inflammation plays an important role in the initiation and progression of cardiovascular disease.[15] An elevated serum level of UA induces inflammation and oxidation stress, and activates the renin-angiotensin-aldosterone system, which may result in cardiac hypertrophy and interstitial fibrosis.[16] On the other hand, it is possible that an elevated serum UA level is an indicator for increased XO activity due to an abnormal energy metabolism connected to cardiomyopathy.[17] Perhaps this corrupt energy mechanism plays an important role in the determination of the type of hypertrophy and electrophysiological structuring. In a recent study, there was a significant relationship between the serum UA level and the LVMI.[18] Similarly, in our study, a significant correlation was observed between the serum UA level and the LVM and LVMI, and between the UA/Cr ratio and the LVMI.

The structural problem in patients with HCM is not only increased LVM, but the LA is also often enlarged in these patients, and its size provides important prognostic information, although most published studies have used the LAAPD.[1,3,19] Previous studies have demonstrated that hyperuricemia is associated with the dilatation of LA size or elevated LA pressure. In the present study, there were significant correlations between serum UA level and the LAAPD, LAMLD, LAABD, and LAVI, as well.

As we mentioned above, progressive cardiac remodeling, which causes irregular and abnormal myocardial hypertrophy along with excessive fibrous tissue accumulation,[20] separates the myocardium into regions where "islands" of viable myocardial tissue establish a ground for the formation of fQRS.[21] fQRS has been demonstrated to be a more sensitive marker with a higher predictive value for myocardial scarring than Q waves on 12-lead ECG.[6] In this study, a significant relationship was observed between the serum UA level and positive fQRS and corrected QT prolongation. Galectin-3, which is secreted by macrophages, is now a hotly debated marker and often associated with poor prognosis in cardiovascular diseases. Although the mechanism is not the same as that of full UA, galectin-3 has been known for its significant role in mediating cardiac fibrosis and inflammation.[22] In our study, the serum galectin-3 level was significantly higher in the patient group than in the control group. Furthermore, a significant correlation was observed between the serum UA level and the galectin-3 level.

Another cause of an elevated UA level in HCM patients may explained by hypoxia. A previous study demonstrated that an increased urinary UA/Cr ratio can be a valuable indicator of the severity of tissue hypoxia as a sign of increased adenosine triphosphate degradation.[23] In HCM patients, hypoxia may develop as a consequence of a supply-demand gap caused by abnormal hypertrophy and a drop in the coronary flow reserve due to microvascular dysfunction, even if there is no significant coronary stenosis.[24,25] A study demonstrated that patients with a high serum UA level had impaired coronary microvascular function.[26] Failure of energy-dependent electrolyte pumps in hypoxia may lead to an intracellular electrolyte imbalance, causing the formation of malignant arrhythmias. In the present study, there was a significant relationship between the serum UA level, the incidence of VT, and the need for CPR and ICD.

The ESC HCM 2014 guideline suggested an easily applicable risk prediction risk model for estimating the risk of SCD in 5 years. According to this model, the risk can be calculated using following values: maximum LV wall thickness, LA size, maximum LVOTO, a family history of SCD, non-sustained VT monitored by Holter or ECG, and presence of unexplained syncope episodes. According to this scale, patients with an HCM Risk-SCD greater than 6% are considered high-risk and ICD implantation is suggested.[1] In our study, patients with a HCM Risk-SCD over 6% also had an increased plasma UA level. Based on this result, it can be suggested that a high serum UA level may be helpful in the pre-evaluation of patients with an increased risk of SCD. However, more studies are needed in this regard.

Study limitations

There are several limitations associated with the present study. The study population was relatively

small and other oxidative stress or inflammation markers were not assessed. Patients aged 18 years and over were included in our study. Pediatric patients and athletes were excluded. A genetic test for HCM could not be performed for all patients; we performed a genetic test in only 3 patients for whom we were unable to establish a definite diagnosis. Therefore, we could not evaluate the relationship of genetic mutation types to UA. Contrast-enhanced cardiac magnetic resonance imaging evaluation could not be performed for all patients because some of the patients did not agree to the procedure, some had an allergy to contrast agents, and some had metal implants in their bodies. Serial UA measurements could not be taken at all of the visits during the follow-up period, so we could not follow changes in the serum UA level. This is an important limitation of the study. The plasma UA level of patients who received septal ablation treatment or a myomectomy was not checked a second time, and therefore, a change in the serum UA level after treatment could not be evaluated. As a final, important disadvantage, the duration of the follow-up of the patients was insufficient.

Conclusion

The serum UA level was significantly higher in patients with HCM compared with the control group. A high serum UA level was associated with a higher HCM-Risk SCD score, positive fQRS on ECG, higher serum galectin-3 level, greater LAAPD, VT incidence, and the need for ICD implantation and CPR in patients with HCM. Based on these results, the serum UA level may provide some information about disease severity and the identification of patients with a high risk for SCD.

Statement of competing interests: There is no disclosure of any interest (financial or otherwise) in this study.

Conflict of interest: There is no disclosure of any interest (financial or otherwise) in this study.

Funding resources: None

Authorship contributions: Concept - S.Ö., Design - S.Ö., M.H.S.; Supervision - S.Ö., O.A.S; Data Collection- S.Ö., H.U., Analysis and/or interpretation -S.Ö., M.G.; Literature search - M.H.S., S. Ö.; Writing - S.Ö.; Critical revision - M.G., H.U., O.A.S.

REFERENCES

1. Authors/Task Force members, Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, et al. 2014 ESC Guidelines on diagnosis and management of hypertrophic cardiomyopathy: the Task Force for the Diagnosis and Management of Hypertrophic Cardiomyopathy of the European Society of Cardiology (ESC). Eur Heart J 2014;35:2733–79. [CrossRef]
2. Kofflard MJ, Ten Cate FJ, van der Lee C, van Domburg RT. Hypertrophic cardiomyopathy in a large community-based population: clinical outcome and identification of risk factors for sudden cardiac death and clinical deterioration. J Am Coll Cardiol 2003;41:987–93. [CrossRef]
3. O'Mahony C, Jichi F, Pavlou M, Monserrat L, Anastasakis A, Rapezzi C, et al. A novel clinical risk prediction model for sudden cardiac death in hypertrophic cardiomyopathy (HCM risk-SCD). Eur Heart J 2014;35:2010–20. [CrossRef]
4. de Boer RA, Lok DJ, Jaarsma T, van der Meer P, Voors AA, Hillege HL, et al. Predictive value of plasma galectin-3 levels in heart failure with reduced and preserved ejection fraction. Ann Med 2011;43:60–8. [CrossRef]
5. Özyılmaz S, Akgül Ö, Uyarel H, Pusuroğlu H, Karayakalı M, Gül M, et al. Assessment of the association between the presence of fragmented QRS and the predicted risk score of sudden cardiac death at 5 years in patients with hypertrophic cardiomyopathy. Anatol J Cardiol 2017;18:54–61. [CrossRef]
6. Das MK, Suradi H, Maskoun W, Michael MA, Shen C, Peng J, et al. Fragmented wide QRS on a 12-lead ECG: a sign of myocardial scar and poor prognosis. Circ Arrhythm Electrophysiol 2008;1:258–68. [CrossRef]
7. Liu T, Zhang X, Korantzopoulos P, Wang S, Li G. Uric acid levels and atrial fibrillation in hypertensive patients. Intern Med 2011;50:799–803. [CrossRef]
8. Hamaguchi S, Furumoto T, Tsuchihashi-Makaya M, Goto K, Goto D, Yokota T, et al; JCARE-CARD Investigators. Hyperuricemia predicts adverse outcomes in patients with heart failure. Int J Cardiol 2011;151:143–7. [CrossRef]
9. Zhu L, Wang J, Wang Y, Jia L, Sun K, Wang H, et al. Plasma Uric Acid as a Prognostic Marker in Patients With Hypertrophic Cardiomyopathy. Can J Cardiol 2015;31:1252–8.
10. Pusuroglu H, Akgul O, Erturk M, Bolat I, Tasbulak O, Ornek V, et al. Assessment of relationship between galectin-3 and ambulatory ECG-based microvolt T-wave alternans in sustained systolic-diastolic hypertension patients. Blood Press Monit 2016;21:265–70. [CrossRef]
11. Schiller NB, Shah PM, Crawford M, DeMaria A, Devereux R, Feigenbaum H, et al. Recommendations for quantitation of the left ventricle by two-dimensional echocardiography. American Society of Echocardiography Committee on Standards, Subcommittee on Quantitation of Two-Dimensional Echocardiograms. J Am Soc Echocardiogr. 1989;2:358–67.
12. Devereux RB, Koren MJ, de Simone G, Okin PM, Kligfield P. Methods for detection of left ventricular hypertrophy: application to hypertensive heart disease. Eur Heart J 1993;14 Suppl D:8–15.
13. Lu W, Song K, Wang Y, Zhang Q, Li W, Jiao H, et al. Rela-

tionship between serum uric acid and metabolic syndrome: an analysis by structural equation modeling. J Clin Lipidol 2012;6:159–67. [CrossRef]

14. Feig DI, Madero M, Jalal DI, Sanchez-Lozada LG, Johnson RJ. Uric acid and the origins of hypertension. J Pediatr 2013;162:896–902. [CrossRef]
15. Ozyilmaz S, Akgul O, Uyarel H, Pusuroglu H, Gul M, Satilmisoglu MH, et al. The importance of the neutrophil-to-lymphocyte ratio in patients with hypertrophic cardiomyopathy. Rev Port Cardiol 2017;36:239–46. [CrossRef]
16. Peraçoli MT, Bannwart CF, Cristofalo R, Borges VT, Costa RA, Witkin SS, et al. Increased reactive oxygen species and tumor necrosis factor-alpha production by monocytes are associated with elevated levels of uric acid in pre-eclamptic women. Am J Reprod Immunol 2011;66:460–7. [CrossRef]
17. Hare JM, Johnson RJ. Uric acid predicts clinical outcomes in heart failure: insights regarding the role of xanthine oxidase and uric acid in disease pathophysiology. Circulation 2003;107:1951–3. [CrossRef]
18. Yamauchi Y, Fujita SI, Shibata K, Morita H, Ito T, Sohmiya K, et al. Is Serum Uric Acid Independently Associated With Left Ventricular Mass Index, Ejection Fraction, and B-Type Natriuretic Peptide Among Female and Male Cardiac Patients? Int Heart J 2017;58:562–9. [CrossRef]
19. Nistri S, Olivotto I, Betocchi S, Losi MA, Valsecchi G, Pinamonti B, et al. Prognostic significance of left atrial size in patients with hypertrophic cardiomyopathy (from the Italian Registry for Hypertrophic Cardiomyopathy). Am J Cardiol 2006;98:960–5. [CrossRef]
20. Iwashima Y, Horio T, Kamide K, Rakugi H, Ogihara T, Kawano Y. Uric acid, left ventricular mass index, and risk of cardiovascular disease in essential hypertension. Hypertension 2006;47:195–202. [CrossRef]
21. Nomura A, Konno T, Fujita T, Tanaka Y, Nagata Y, Tsuda T, et al. Fragmented QRS predicts heart failure progression in patients with hypertrophic cardiomyopathy. Circ J 2015;79:136–43. [CrossRef]
22. Amin HZ, Amin LZ, Wijaya IP. Galectin-3: a novel biomarker for the prognosis of heart failure. Clujul Med 2017;90:129–32. [CrossRef]
23. Bhongir AV, Yakama AV, Saha S, Radia SB, Pabbati J. The Urinary Uric Acid/Creatinine Ratio is An Adjuvant Marker for Perinatal Asphyxia. Eur J Pharm Med Res 2015;2:520–8.
24. Cannon RO 3rd, Schenke WH, Maron BJ, Tracy CM, Leon MB, Brush JE Jr, et al. Differences in coronary flow and myocardial metabolism at rest and during pacing between patients with obstructive and patients with nonobstructive hypertrophic cardiomyopathy. J Am Coll Cardiol 1987;10:53–62.
25. Camici P, Chiriatti G, Lorenzoni R, Bellina RC, Gistri R, Italiani G, et al. Coronary vasodilation is impaired in both hypertrophied and nonhypertrophied myocardium of patients with hypertrophic cardiomyopathy: a study with nitrogen-13 ammonia and positron emission tomography. J Am Coll Cardiol 1991;17:879–86. [CrossRef]
26. de A Coutinho T, Turner ST, Kullo IJ. Serum uric acid is associated with microvascular function in hypertensive individuals. J Hum Hypertens 2007;21:610–5. [CrossRef]

Keywords: Cardiomyopathy; hypertrophic; risk; sudden cardiac death; uric acid.

Anahtar sözcükler: Kardiyomiyopati; hipertrofik; risk; ani kardiyak ölüm; ürik asit.